

# Competing-Risk Analysis of ESRD and Death among Patients with Type 1 Diabetes and Macroalbuminuria

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## ABSTRACT

Patients with both type 1 diabetes and CKD have an increased risk of adverse outcomes. The competing risks of death and ESRD may confound the estimates of risk for each outcome. Here, we sought to determine the major predictors of the cumulative incidence of ESRD and pre-ESRD mortality in patients with type 1 diabetes and macroalbuminuria while incorporating the competing risk for the alternate outcome into a Fine-Gray competing-risks analysis. We followed 592 patients with macroalbuminuria for a median of 9.9 years. During this time, 56 (9.5%) patients died and 210 (35.5%) patients developed ESRD. Predictors of incident ESRD, taking baseline renal function and the competing risk for death into account, included an elevated HbA<sub>1c</sub>, elevated LDL cholesterol, male sex, weight-adjusted insulin dose, and a shorter duration of diabetes. By contrast, predictors of pre-ESRD death, taking baseline renal function and the competing risk for ESRD into account, included only age, the presence of established macrovascular disease, and elevated cholesterol levels. This competing-risks approach has potential to highlight the appropriate targets and strategies for preventing premature mortality in patients with type 1 diabetes.

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The presence of overt nephropathy in patients with type 1 diabetes from Finland is associated with an increased risk of premature mortality that is over nine times that observed in the age-gender matched general population.<sup>1</sup> A number of different factors potentially contribute to this risk, including poor glycemic control and dyslipidemia. Epidemiologic understanding of the role different factors may play in these adverse outcomes has potentially been limited by cause-specific analyses that fail to take into account competing risks.<sup>2</sup> In particular, in individuals with macroalbuminuria, the outcomes of death and ESRD have important competing effects. For example, analysis of the predictors of ESRD needs to take into account the risk of dying before ESRD. Equally, the consequence of analyzing the predictors of death while taking into account the (proxi-

mal) risk of ESRD effectively limits exposure time to the pre-ESRD milieu and “hastens” exposure to the different risks associated with renal replacement therapy. This kind of analysis may be best performed within the paradigm of a formal competing-risks (Fine-Gray) proportional-hazards regression model, which estimates the cumulative incidence of an outcome while accounting for the competing risks of an

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**Table 1.** Clinical characteristics of patients with type 1 diabetes and macroalbuminuria from the FinnDiane cohort, divided by outcomes

| Baseline Parameters                    | Alive without ESRD, n = 326 | ESRD, n = 210                 | Dead without ESRD, n = 56     |
|--|-----------------------------|-------------------------------|-------------------------------|
| Men, n (%)                             | 186 (57%)                   | 131 (62%)                     | 35 (63%)                      |
| Age (years)                            | 40.5 ± 9.9                  | 41.6 ± 9.3                    | 47.7 ± 12.3 <sup>a</sup>      |
| Duration of diabetes (years)           | 29.1 ± 8.1                  | 28.9 ± 8.0                    | 32.8 ± 8.2 <sup>a</sup>       |
| Body mass index (kg/m <sup>2</sup> )   | 26.1 ± 3.6                  | 25.6 ± 4.5 <sup>a</sup>       | 26.4 ± 4.6                    |
| WHR                                    | 0.89 ± 0.08                 | 0.91 ± 0.09                   | 0.93 ± 0.09 <sup>a</sup>      |
| eGDR (mg/kg/min)                       | 4.4 ± 1.8                   | 3.7 ± 1.6 <sup>a</sup>        | 3.9 ± 1.8 <sup>a</sup>        |
| Ever smoking n (%)                     | 186 (57%)                   | 135 (64%) <sup>a</sup>        | 37 (65%)                      |
| Macrovascular disease, n (%)           | 45 (14%)                    | 45 (21%)                      | 20 (36%) <sup>a</sup>         |
| Laser treatment, n (%)                 | 253 (78%)                   | 176 (84%)                     | 44 (78%)                      |
| HbA <sub>1c</sub> (%)                  | 8.8 ± 1.4                   | 9.4 ± 1.6 <sup>a</sup>        | 9.0 ± 1.4                     |
| Insulin dose (units per kg)            | 0.71 ± 0.23                 | 0.64 ± 0.20 <sup>a</sup>      | 0.66 ± 0.23                   |
| Antihypertensive medication n (%)      | 305 (94%)                   | 205 (98%)                     | 54 (96%)                      |
| Systolic blood pressure (mmHg)         | 140 ± 17                    | 150 ± 21 <sup>a</sup>         | 150 ± 22 <sup>a</sup>         |
| Diastolic blood pressure (mmHg)        | 82 ± 10                     | 84 ± 10                       | 80 ± 10                       |
| Lipid-lowering medication n (%)        | 59 (18%)                    | 73 (35%) <sup>a</sup>         | 11 (20%)                      |
| Total cholesterol (mmol/L)             | 5.2 ± 0.9                   | 5.6 ± 1.2 <sup>a</sup>        | 5.6 ± 1.0 <sup>a</sup>        |
| LDL cholesterol (mmol/L)               | 3.3 ± 0.8                   | 3.5 ± 1.1 <sup>a</sup>        | 3.5 ± 1.0                     |
| Triglycerides (mmol/L)                 | 1.2 (0.9 to 1.7)            | 1.7 (1.2 to 2.4) <sup>a</sup> | 1.5 (1.2 to 2.3) <sup>a</sup> |
| HDL cholesterol (mmol/L)               | 1.2 ± 0.4                   | 1.2 ± 0.3                     | 1.2 ± 0.4                     |
| eGFR (ml/min per 1.73 m <sup>2</sup> ) | 67 ± 23                     | 32 ± 19 <sup>a</sup>          | 58 ± 24 <sup>a</sup>          |

Data are means with SD or medians with interquartile range. WHR, waist-to-hip ratio; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate.

<sup>a</sup>Versus alive without ESRD, P < 0.05.

alternative outcome.<sup>3</sup> To better understand how traditional risk factors may be functioning in our patients, the present work aims to determine the major predictors of the cumulative incidence of ESRD and pre-ESRD mortality in patients with type 1 diabetes and macroalbuminuria, while incorporating the competing event(s) of the alternate outcome into a competing-risks analysis.<sup>4</sup>

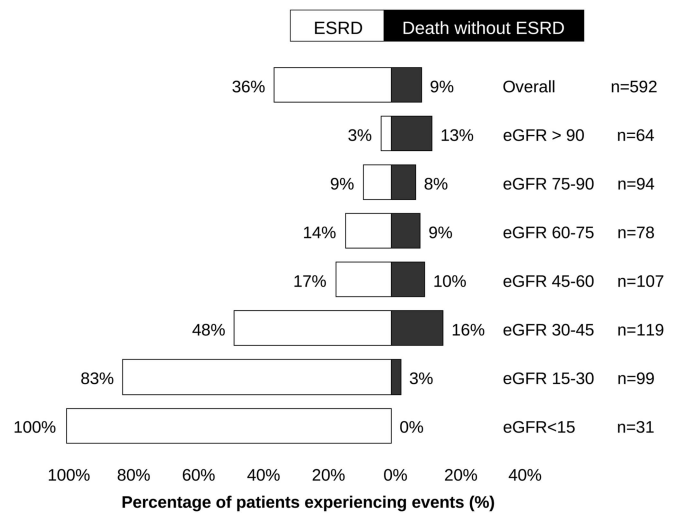
**RESULTS**

**Cohort Characteristics**

Outcomes were determined in 592 participants from the FinnDiane study with type 1 diabetes and a urinary albumin excretion in the macroalbuminuric range. Their baseline characteristics have been previously described in detail<sup>1,5,6</sup> and are summarized in Table 1. Briefly, 59% of patients were men (n = 352). The mean age of participants was 42 years with a median duration of diabetes of 29 years. At baseline, 20% of the cohort had pre-existing macrovascular disease. Sixty percent of patients with macroalbuminuria had an eGFR <60 ml/min per 1.73 m<sup>2</sup>, denoting the presence of moderate to severe renal impairment. Despite the use of insulin regimens and multiple antihypertensive and lipid-lowering therapies, less than half of all patients achieved standard therapeutic targets. In particular, 45% of patients had an HbA<sub>1c</sub> >9.0%. Seventy-five percent of patients had a systolic BP >130 mmHg and 70% of patients had a LDL cholesterol >3.0 mmol/L.

**Predictors of the Cumulative Incidence of ESRD**

During a median of 9.9 years of follow-up, 210 individuals developed ESRD (36%; incidence rate of ESRD of 5.1 per hundred person-years (95% confidence interval [CI] 4.44, 5.85). Patients who developed ESRD during follow-up had lower baseline renal function and worse control of their blood glucose, lipid, and BP levels (Table 1). Fifty-six participants died without first developing ESRD. After the competing risk of death (Figure 1) was taken into account, predictors of increased cumulative incidence of ESRD in patients with established macroalbuminuria were a reduced baseline estimated GFR (eGFR), elevated LDL cholesterol, elevated HbA<sub>1c</sub>, a shorter duration of diabetes, male gender, and the weight-adjusted insulin dose (all P < 0.01; Table 2). After adjusting for other risk factors and accounting for the competing risk of death, male individuals (compared with women, subhazard ratio = 1.96 [95% CI 1.39, 2.76]) with the worst renal function were more likely to develop ESRD than those with modest or mild impairment (Figures 1 and 2). Achieved glycemic control at baseline, as denoted by the HbA<sub>1c</sub>, and poor control of LDL cholesterol levels were linearly associated with the cumulative incidence of ESRD (Table 2). Non-linear associations were also observed between body mass index and adjusted insulin dose and the incidence of ESRD (Table 2, Figure 2). Notably, the univariate association of BP and ESRD was eliminated after adjusting for baseline



**Figure 1.** Incidence of ESRD and pre-ESRD mortality, stratified for renal function at baseline, shows the impact of competing risks.

**Table 2.** Competing-risk model of variables associated with the cumulative incidence of ESRD in patients with type 1 diabetes and macroalbuminuria from the FinnDiane cohort

| Predictor Variables               | Subhazard Ratio | [95% CI]     | P     |
|-----------------------------------|-----------------|--------------|-------|
| Men                               | 1.96            | 1.39 to 2.76 | 0.001 |
| Estimated GFR (FP) <sup>a</sup>   | 0.05            | 0.04 to 0.07 | 0.001 |
| LDL cholesterol (FP) <sup>a</sup> | 1.01            | 1.00 to 1.01 | 0.001 |
| Duration of diabetes (years)      | 0.97            | 0.95 to 0.99 | 0.028 |
| HbA <sub>1c</sub> (%)             | 1.31            | 1.15 to 1.48 | 0.001 |
| Body mass index (FP) <sup>a</sup> | 281             | 5.13 to 1548 | 0.006 |
| Insulin dose (FP) <sup>a</sup>    | 0.87            | 0.79 to 0.97 | 0.010 |
| Insulin dose (FP) <sup>a</sup>    | 0.30            | 0.13 to 0.69 | 0.005 |

For graphical interpretation, see Figure 2. FP, fractional polynomial. Fractional polynomials are extensions of the conventional polynomial, allowing unique and repeated powers of a (positive) continuous variable, the powers being (−2, −1, −0.5, 0, 0.5, 1, 2, 3) and the power 0 = logarithm. Thus, a 2,2 fractional polynomial has the general form:  $\beta_0 + \beta_1x^2 + \beta_2x^2 \log x$ , where  $\beta_0$  is the intercept and  $x$  the continuous covariate.<sup>26</sup> Duration of diabetes and HbA<sub>1c</sub> are parameterized as linear variables. Baseline category for gender = female. The coefficient effects represented by FP are not subject to literal effect interpretation (compared with other coefficients) as the underlying scale was further transformed in the process of FP generation.

<sup>a</sup>GFR, 0 (log); LDL cholesterol, 3rd degree; body mass index, −2; insulin dose, −2.3.

renal function. No time-varying covariate effect was demonstrated ( $P \geq 0.11$ ) and there were no unduly influential observations across the covariates; no significant interactions were demonstrated.

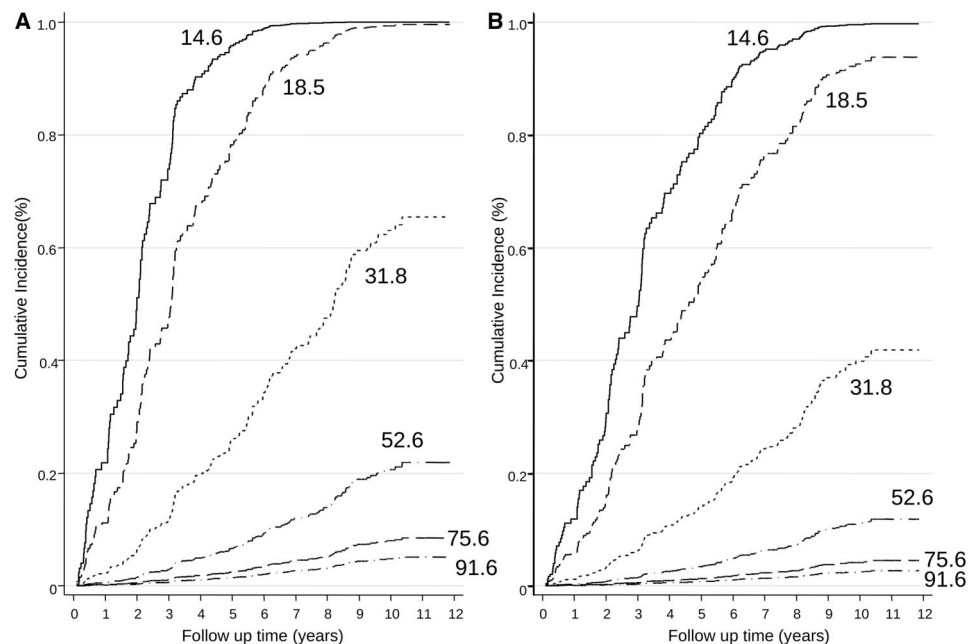
### Predictors of the Cumulative Incidence of Pre-ESRD Mortality

Fifty-six participants died without first developing ESRD. After the competing risk of ESRD is taken into account, the predictors of the cumulative incidence of death before ESRD were older age

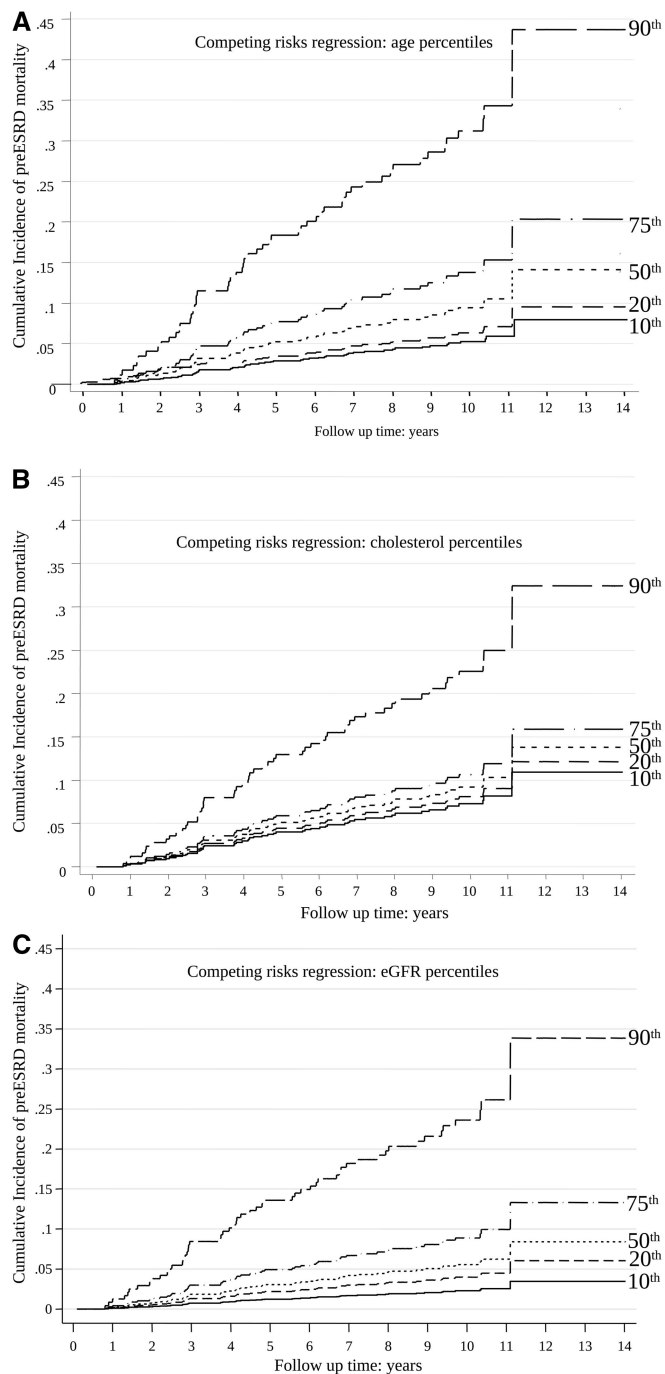
(Figure 3A), the presence of established macrovascular disease (as an interaction term), elevated cholesterol levels (Figure 3B), and renal function (as eGFR; Figure 3C, Table 3). The effect of baseline renal function was nonlinear (parameterized as a 3rd-degree regression spline), reflecting lead time in the “real world” setting where individuals with the lowest eGFR are more likely to reach ESRD than die, whereas those with more preserved renal function were more likely to die than reach ESRD (Figure 1). The model was well specified with no unduly influential observations. The effect of total cholesterol, when tested with other covariates, exhibited a time-varying effect of borderline significance ( $P = 0.05$ ). However, the global test for (lack of) proportionality for time-varying covariates was NS ( $P = 0.33$ ).

### DISCUSSION

Patients with type 1 diabetes who have macroalbuminuria have an increased risk of both ESRD and death.<sup>1,7</sup> These outcomes have important competing effects that potentially confound a cause-specific analysis. In contradistinction to the latter form of analysis, we have developed a formal competing-risks (Fine-



**Figure 2.** Increasing cumulative incidence of ESRD with lower baseline levels of eGFR, stratified for gender [men (A) women (B)], adjusted to the mean of other variables. Estimated GFR has been stratified by percentiles: 5th (eGFR = 14.6; solid line); 10th (eGFR = 18.5; short dashed line); 25th (eGFR = 31.8; dotted line); 50th (eGFR = 52.6; long-dash dot line); 75th (eGFR = 75.6; long-dash line); 90th (eGFR = 91.6; short-dash dot line); men, left panel; women, right panel.



**Figure 3.** Cumulative incidence of pre-ESRD death increases with increasing age (A), total cholesterol levels (B), and increasing eGFR (C). Data is adjusted to the mean of other variables.

Gray) model that looks at the cumulative incidence of an ESRD or death before ESRD while also taking into consideration (in an estimation sense) competing risk of the alternate outcome. Although widely used to evaluate mortality in intensive care and cancer studies, this form of analysis is novel to renal studies but one that has great relevance to the epidemiologic study of chronic kidney disease (CKD).

In many previous analyses, including our own,<sup>1</sup> the predic-

tors of mortality in patients with CKD have been explored, regardless of the timing of the mortality event. For example, in patients with macroalbuminuria at baseline from the FinnDiane study more individuals died subsequent to the development of renal impairment sufficient to require renal replacement ( $n = 65$ ) than died before reaching ESRD ( $n = 56$ ). In our previous analysis,<sup>1</sup> we pooled pre- and post-ESRD deaths, although the contributing factors may be significantly different (such as timing and mode of dialysis, type of transplantation, etc.). Consequently, in the present study, we deliberately examined only the specific outcome of pre-ESRD mortality, with the specific aim of determining those risk factors that are independently associated with this outcome, without the confounding effects of renal replacement management and other factors that may affect outcomes during the provision of these therapeutic modalities.

Briefly, the mechanics of a formal competing-risk regression analysis are these: the event of interest (say, ESRD) is nominated and entered into a proportional-hazards regression and appropriate predictors are determined for the cumulative incidence. In a cause-specific analysis (using, for example, Cox regression) only the “pure” effect of ESRD would be estimated. Patients who died before ESRD would therefore be censored or alternatively considered to be event-free. Consequently, conventional cause-specific analysis can readily lead to *biased* estimates. By contrast, in a competing-risks analysis, these patients (and their survival time to the competing event) are carried forward (they are not censored) in the risk set and appropriately accounted for, by appropriate weighting, in a bivariate analysis. Not only does such an approach better reflect the “real-world” relationship between covariates and specific outcomes but also potentially allows the true relationship between clinically relevant parameters and outcomes to be legitimately described.<sup>4,8,9</sup>

In this cohort, glycemic control was linearly related to the cumulative incidence of ESRD. We previously demonstrated that glycemic control is also associated with all-cause mortality in patients with CKD.<sup>1</sup> However, in our new competing-risks analysis, HbA<sub>1c</sub> was not associated with the cumulative incidence of mortality pre-ESRD. It is therefore possible to speculate that poor glycemic control increases all-cause mortality in type 1 diabetes predominantly by promoting progression to ESRD. Furthermore, any studies that censored ESRD patients or had few progressors may therefore have observed no mortality risk associated with HbA<sub>1c</sub><sup>10,11</sup>. For example, the lack of association between HbA<sub>1c</sub> and mortality in the Diabetes Control and Complications Trial (DCCT) trial may be partly because of the low incidence of ESRD.<sup>12</sup> In addition, recent large studies in patients with type 2 diabetes in which glucose control failed to improve mortality outcomes were too short to show effects on ESRD and its associated mortality therein.<sup>13</sup>

Unlike glycemic control, cholesterol levels were significantly associated with mortality before ESRD as well as the competing outcome of ESRD itself. Although inference with respect to time-varying effects (of cholesterol) is problematic in the Fine-Gray paradigm,<sup>14</sup> this association is consistent with



**Table 3.** Competing-risk model of variables associated with the cumulative incidence of death prior to ESRD in patients with type 1 diabetes and macroalbuminuria from the FinnDiane cohort. For graphical interpretation, see Figure 3

| Baseline Parameter                       | Subhazard Ratio | [95% CI]     | <i>P</i> > <i>t</i> |
|--|-----------------|--------------|---------------------|
| Age (years)                              | 1.05            | 1.02 to 1.07 | 0.001               |
| Total cholesterol (mmol/L)               | 1.75            | 1.17 to 2.61 | 0.007               |
| Macrovascular disease (yes/no) × age     | 1.01            | 1.00 to 1.03 | 0.03                |
| eGFR (standardized) <sup>a</sup>         | 2.12            | 1.25 to 3.58 | 0.005               |
| eGFR (orthogonalized basis) <sup>a</sup> | 1.59            | 0.92 to 2.76 | 0.09                |
| eGFR (orthogonalized basis) <sup>a</sup> | 0.56            | 0.36 to 0.88 | 0.01                |

<sup>a</sup>eGFR was parameterized as a 3rd-degree (cubic) regression spline with knots at 32.1 and 52.9. The parameterization of the spline is thus: a spline with *m* knots has *m* + 1 so-called basis functions (and similar degrees of freedom) and these basis functions are orthogonalized to have mean 0 and SD 1 and to be uncorrelated.<sup>28</sup>

a number of previous studies in which the accumulation of small dense LDL in patients with proteinuria is associated with adverse outcomes<sup>15,16</sup> including both mortality and renal progression.<sup>17</sup> Although a causal link remains to be established, recent findings in statin trials have demonstrated clear improvements in pre-ESRD mortality rates as well as the incidence of ESRD.<sup>18,19</sup> In this cohort, it is clear that statins have been underutilized and cholesterol lowering presents a potential means to prevent pre-ESRD death as well as ESRD itself.

Body mass was also a predictor of the cumulative incidence of ESRD in this cohort. Although this association was independent of baseline renal function adjusted for surface area, it is possible to speculate that smaller individuals have lower renal function or lower renal mass for the same eGFR, leading to increased demand and more rapid burnout, when compared with larger individuals with the same eGFR. The association between body mass and ESRD was not demonstrated to be due to insulin resistance, as insulin dose was independently associated with the incidence of ESRD (Table 2) and estimated glucose disposal rate was not associated with incidence after adjusting for the HbA<sub>1c</sub>.

One key strength of this study is the large number of ESRD events. Modern improvements in diabetes care and cardiovascular survival have meant that many patients with type 1 diabetes live long enough to require renal replacement. In our cohort, ESRD was by far the most likely outcome (Figure 2A), with 36% of patients developing ESRD during follow-up (*n* = 210). This equates to an incidence of 5.1 per 100 person-years (95% CI 4.44, 5.85), and is comparable to that observed in German patients with macroalbuminuria (35%)<sup>20</sup> and in line with some more contemporary data from the Joslin Diabetes Center, where the incidence of ESRD was 5.3 per 100 person-years in patients with proteinuria.<sup>21</sup> These data suggest that our ability to slow down overt nephropathy is limited at best, and has not improved substantially since the advent of the renin-angiotensin system blockade. Moreover, these data support the urgent need to identify new targets for intervention in those with overt renal disease.

Another key strength of this study is our ability to adjust for

the nonlinear associations between eGFR and adverse outcomes. In traditional analysis, the severity of renal impairment at baseline is a major confounding factor, largely reflecting the “proximity” or lead time of patients with lower renal function to ESRD and its associated risk of death. As a lower renal function at baseline favors the development of ESRD, it consequently confounds interpretation of its competing risk, that of death before ESRD. Equally, preserved renal function at baseline means that death is a much more likely outcome than ESRD. By modeling and preserving these complex interactions, we have potentially

been able to better demonstrate other predictors of ESRD and premature mortality, and the shape of their relationship to these adverse outcomes.

Other strengths of the FinnDiane study include its large cohort of individuals with type 1 diabetes, high participation rate, long follow-up period, access to subsidized care (75 to 100% of costs), and contemporary treatment regimens, including a range of insulin regimens, statins, blockers of the renin-angiotensin system, and self-monitoring technologies. We used validated methods to identify deaths and all deaths in our cohort were confirmed through death records. Surveillance bias is unlikely given the uniform vital status follow-up procedures used by our staff masked to participants' CKD status levels. In our questionnaire, we had broad data on tobacco or alcohol use, diet, education, socioeconomic status, other possible confounders, or the severity of disease. Although eGFR is a less than optimal predictor of true renal function, the majority of our patients had moderate to severe renal impairment (eGFR <60 ml/min per 1.73 m<sup>2</sup>) where the Modification of Diet in Renal Disease (MDRD) equation works better (although not perfectly). Finally, few changes in diabetes treatment and health care over the short study period affected mortality results. Nonetheless, during the follow-up time period some new treatment options appeared and treatment targets became stricter. Assuming that these changes improved the prognosis, we may thus have overestimated the incidence of ESRD and mortality today.

In conclusion, despite aggressive treatment, many patients with type 1 diabetes and overt nephropathy develop ESRD and/or succumb to a premature death. In our cohort, ESRD was the most likely outcome, potentially driving epidemiologic associations between risk factors and all-cause mortality. By adjusting for these competing risks, we show that poor glycaemic control increases the cumulative incidence of ESRD, but is not associated with increased pre-ESRD mortality. By contrast, improved lipid control may affect both ESRD outcomes and pre-ESRD mortality. This kind of novel statistical approach has the potential to shed new light on the targets and strategies for preventing premature mortality in patients with type 1 diabetes.

## CONCISE METHODS

### Study Sample

This study is part of the ongoing prospective nationwide multicenter Finnish Diabetic Nephropathy (FinnDiane) Study, with the aim to identify genetic, clinical, and environmental risk factors for diabetic nephropathy in patients with type 1 diabetes.<sup>1,5,6</sup> Type 1 diabetes was defined as an onset of diabetes before the age of 40 years and permanent insulin treatment initiated within 1 year of diagnosis. For this study, outcomes were ascertained in patients in the FinnDiane prospective cohort with type 1 diabetes and macroalbuminuria ( $n = 592$ ). This was defined by an albumin excretion rate (AER)  $\geq 200$   $\mu\text{g}/\text{min}$  or  $\geq 300$   $\text{mg}/\text{d}$  in at least 2 of 3 consecutive overnight or 24-hour urine samples. None of these individuals had ESRD at baseline. These baseline assessments were performed between 1995 and 2006. The ethical committees of all participating centers approved the study protocol. Written informed consent was obtained from each patient and the study was performed in accordance with the Declaration of Helsinki as revised in the year 2000.

### Cohort Characteristics

At baseline, all patients also underwent a thorough clinical investigation in connection with a regular patient visit to their attending physician. Data on medication and diabetic complications were registered with the use of a standardized questionnaire, which was completed by the physician based upon medical files. BP was measured twice in the sitting position after a 10-minute rest and the average of these two measurements were used in the analysis. Height, weight, and waist-to-hip ratio were recorded and blood was drawn for the measurement of HbA<sub>1c</sub>, lipids, and creatinine. Macrovascular disease was defined as a history of myocardial infarction, a coronary artery procedure (bypass surgery or angioplasty), stroke, limb amputation, or peripheral artery procedure, which was verified from the medical files. HbA<sub>1c</sub> was determined by standardized assays at each center. Serum lipid and lipoprotein concentrations were analyzed centrally by automated enzymatic methods (Hoffmann-LaRoche, Basel, Switzerland). Serum creatinine was measured with Jaffé's method until January 7, 2002, and thereafter by enzymatic methods at a central laboratory. The values from the two methods were highly correlated with an  $R^2 = 0.977$ . The GFR was consequently estimated (eGFR) with the original MDRD-4 equation until 2002,<sup>22</sup> and with the revised MDRD-4 equation after that.<sup>23</sup>

### Ascertainment of Outcomes

Deaths from any cause through to March 24, 2009, were identified via a search of the Finnish National Death Registry, and center databases. All deaths were confirmed with death certificate data. In each case, vitality status was verified from the Finnish National Death Registry. ESRD was defined as the requirement for dialysis or kidney transplantation, and identified via a search of the renal registries and center databases and verified from medical files.

### Statistical Analysis

In this paper, we aimed to identify the predictors of the cumulative incidence of ESRD or pre-ESRD death with the Fine and Gray

model,<sup>3</sup> which extends the Cox proportional hazards model to competing-risks data by considering the subdistribution hazard.<sup>2</sup> That is, we limit our analysis to the consideration of two (competing) events: (the development of) ESRD and pre-ESRD deaths; deaths occurring after the development of ESRD are not considered in this analysis. The strength of the association between each predictor variable and the outcome was assessed using the subhazard ratio,<sup>14</sup> which is the ratio of hazards associated with the cumulative incidence function (CIF) in the presence of and in the absence of a prognostic factor. The peculiar advantage of the Fine-Gray approach is that "...while the cumulative incidence function is an involved function of all cause-specific hazards, the subdistribution hazard reestablishes a one-to-one relationship and consequently offers a summarizing analysis of separate cause specific hazards analyses."<sup>8</sup> That is, our motivation was to model the cumulative incidence of, say, ESRD, which is a nonlinear function of both cause-specific hazards (and the baseline hazard):  $h_1(t) \equiv \text{ESRD}$  and  $h_2(t) \equiv \text{death}$ ; as opposed to an approach of, say,  $[1 - (\text{Kaplan-Meier estimate})]$ , which considers the CIF as a function only of  $h_1(t)$ .<sup>24</sup> Importantly, covariates may affect  $h_1$  and  $h_2$  differently. As opposed to a cause-specific analysis, which would censor the competing event(s), the Fine-Gray approach "carries forward" the competing event(s) in the risk set, with appropriate weighting, and does not censor them. The Fine-Gray model assumes proportional hazards, and because of inferential problems associated with the incorporation of time-varying covariates when death is a competing event,<sup>8,9</sup> such covariate function was utilized in a heuristic sense to demonstrate nonproportional hazards. In a Cox regression a "similar" analysis (say, the consideration of pre-ESRD deaths, with ESRD as a competing risk) can be undertaken by prolonging the survival time of the patients with ESRD well beyond the last recorded time of death of the pre-ESRD deaths.<sup>25</sup> In the Cox model, as opposed to a parametric survival model, only events are determinant, as the baseline hazard is not estimated.<sup>25</sup> The potential for covariate multiple colinearity was tested using the variance inflation factor (VIF) and condition number (CN), where  $\text{VIF} < 10$  and  $\text{CN} < 30$  are desirable. As standard errors of the Fine-Gray model are robust (Huber-White type), model selection was guided by information criteria (Akaike [AIC] and Bayesian information criterion [BIC]), not likelihood ratios. Clinically plausible combinations of the initial modest variable ensemble ( $n = 20$ ; see Table 1) were used in model building guided by minimization of information criteria; simple interactions were explored but higher order interactions were not entertained. The model specification was established by residual analysis, DFBETA measures of influence across each model covariate, and formal check of proportionality by the use of time-varying covariate effect;<sup>2</sup> the proportionality was tested across variables by a global ( $\chi^2$ ) test that all time-varying coefficients were 0. Nonlinear covariate effect was explored using both multivariate fractional polynomials and regression splines.<sup>26,27</sup> Parameterization of the fractional polynomial(s) initially considered all powers ( $-2, -1, -0.5, 0, 0.5, 1, 2, 3$ ); that is, the degrees of freedom were initially set at 4. For the regression spline, only a 3rd-degree form was considered. The Fine-Gray model was implemented in Stata statistical software (V11, 2009; College Station, TX) using the "stcrreg" mod-

ule; fractional polynomials were implemented by the “mfp” module. The regression spline was implemented using the user written Stata module “mvsr”.<sup>27</sup> As the Fine-Gray model is a nonlinear bivariate regression model, interpretation of the covariate effect across the range of covariate values is not facile, as for any nonlinear regression model.<sup>27,28</sup> This particularly applies to the “simple” interpretation of the effect of the fractional polynomial and spline regression coefficients; thus, appropriate graphical display has been undertaken to explore effect across the covariate space. These coefficients are appropriately reported with other more conventional variable coefficients in appropriate tables.

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## DISCLOSURES

None.

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- See related editorial, "Is Treatment of Nephropathy in Type 1 Diabetes Efficacious but Ineffective?" on pages 402–404.